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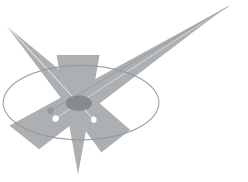

Original Paper

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Postoperative treatment of patients with anaplastic oligodendrogliomas. Thirty years' experience of the Maria Sklodowska-Curie Memorial Centre in Kraków, 1975–2000

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background Anaplastic oligodendrogliomas (AO) are infiltrative, mostly supratentorial tumours, often bilaterally affecting the white matter. Radiotherapy alone or in combination with chemotherapy have a role in the adjuvant treatment of AO, but currently the efficacy of various treatment modalities could not be definitively determined because of the heterogeneity of the therapies used.

Aim Assessment of the efficacy of altered therapy schedules in postoperative treatment of patients with anaplastic oligodendrogliomas

Materials/Methods Between 1975 and 2000, 101 adult patients with anaplastic oligodendrogliomas were postoperatively treated in our institution. During this period patients received conventional radiation therapy and chemotherapy (CRT/CH), conventional radiation therapy (CRT), and split course hypofractionated radiation therapy (SCHRT).

Between 1975 and 1985, CRT/CH was applied in 42 patients. Whole brain irradiation was delivered; the tumour dose of 5Gy in 25 fractions over 5 weeks was calculated at the midplane of the skull. Then treatment fields were reduced and a 10Gy boost was given in 5 fractions over 5 days to the known tumour bearing area. On the last day of irradiation patients began the first of six planned series of chemotherapy with CCNU, given 100mg/², orally every 8 weeks. From 1986 to 1990, CRT was received by 27 patients. Irradiation was only as described above. Between 1991 and 2000, 32 patients were given SCHRT. There were 3 courses of irradiation separated by a one-month interval. In each of the two first series patients received 20Gy in 5 fractions in five days to the whole brain, and in the third course a 20Gy boost in 5 fractions over 5 days was given as in the CRT regimen.

Results Actuarial overall survival rates at two and five years were 38% and 10% respectively for patients treated with CRT/CH, 36% and 11% for the CRT group, and 23% and 6% for the SCHRT option. Multivariate analysis revealed that only age was a significant factor. Patients aged 45 years or less carried the best prognosis.

Conclusions The efficacy of different postoperative treatments administered to our patients with anaplastic oligodendrogliomas gave approximately comparable and unrewarding poor results.

Key words **anaplastic oligodendroglioma • radiation therapy • chemotherapy**

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Background

Approximately 5% of all primary brain tumours are of oligodendroglial tissue. The anaplastic variant, representing about 30% of all oligodendrogliomas, is a markedly densely cellular tumour with pleomorphic nuclei, frequent mitotic activity, vascular proliferation and occasional giant cells. According to the WHO classification, the detection of necrosis in an anaplastic oligodendroglial tumour per se does not make it a glioblastoma. The exact delineation of low- and high-grade (anaplastic) oligodendroglioma is somewhat unclear. The diagnosis of oligodendroglioma is based on histological verification of a tumour sample. In addition to histological analysis, fluorescent *in situ* hybridization (FISH) or loss of heterozygosity (LOH) to detect losses on 1p or 19q may be added to make the diagnosis. It should be admitted at this point, however, that final diagnosis as defined by WHO does not yet include these molecular properties. Anaplastic oligodendrogliomas (AO) are infiltrative, mostly supratentorial tumours which frequently originate in the frontal lobes (50%), often bilaterally affecting the white matter. Corpus callosum and basal ganglia may also be involved [1,2].

Radiotherapy alone or in combination with chemotherapy have a role in the adjuvant treatment of AO, but currently the efficacy of various treatment modalities could not be definitively determined because of the heterogeneity of the therapies used [3].

Aim

The objective of this study is to evaluate the efficacy of altered therapy schedules in the postoperative management of patients with AO.

Materials and Methods

Patients

The study population was derived from neurosurgical centres which referred patients to the Maria Sklodowska-Curie Memorial Centre in Kraków. Surgery consisted of as complete tumour removal as was feasible. All surgical specimens were evaluated by the same pathologist according to the WHO classification. The diagnosis of AO was made based on histological criteria including the presence of oligodendroglial morphology, hypercellularity, nuclear pleomorphism and mitotic activity [4]. Low-grade oligodendrogliomas and anaplastic mixed gliomas were excluded.

Methods

Between 1975 and 2000, 101 adult patients with AO were treated according to one of the three protocols used at our institution. During this period, the treatment modalities were as follows: conventional radiation therapy and chemotherapy (CRT-CH), conventional radiation therapy (CRT), and split course hypofractionated radiation therapy (SCHRT).

Megavoltage irradiation (Cobalt-60 unit or linear accelerator) was started from four to six weeks after surgery.

Between 1975 and 1985 CRT/CH was applied. Whole brain irradiation delivered to a tumour dose of 50Gy in 25 fractions over 5 weeks was calculated at the midplane of the skull. Then, the treatment fields were reduced to cover the known tumour bearing area and a 10Gy "boost" was given in 5 fractions over 5 days. On the last

Table 1. Patient characteristics by the treatment option.

Characteristics	CRT/CH	CRT	SCHRT
Number of patients	42	27	32
Gender			
Male	25 (59%)	17 (63%)	21 (65%)
Female	17 (41%)	10 (37%)	11 (35%)
Age (years)			
45 and less	23 (55%)	13 (48%)	13 (41%)
More then 45	19 (45%)	14 (52%)	19 (59%)
Surgery			
Partial resection	29 (69%)	21 (78%)	22 (68%)
Total resection	13 (31%)	6 (22%)	10 (32%)
Tumor location			
Frontal	19 (46%)	10 (37%)	17 (53%)
Temporal	12 (28%)	8 (30%)	8 (25%)
Elsewhere	11 (26%)	9 (33%)	7 (22%)
Karnofsky's status			
More than 60%	28 (66%)	21 (77%)	23 (72%)
60%	14 (34%)	6 (23%)	9 (28%)

CRT/CH – conventional radiotherapy and chemotherapy; CRT – conventional radiotherapy; SCHRT – split course hypofractionated radiotherapy.

day of irradiation, patients began the first of the six series of chemotherapy. CCNU was given 100mg/m^2, orally every 8 weeks.

1986–1990, CRT: irradiation only as described above.

1991–2000 SCHRT: there were 3 courses of irradiation separated by a one-month interval. In each of the two first series patients received 20Gy in 5 fractions over 5 days to the whole brain, and in the third course a 20Gy "boost" in 5 fractions over 5 days was given as in the CRT regimen.

Patients' characteristics by treatment option are presented in Table 1.

There was some disparity between the characteristics of patients with more frontal tumours and relatively more partial resections in the CRT group. On the basis of the final results of multivariate analysis, it was confirmed that these two parameters (extent of surgery and tumour location) did not affect patient's survival.

Table 2. Tolerance according to treatment schedule.

Tolerance	CRT/CH (42 pts)	CRT (27 pts)	SCHRT (32 pts)
Very good	35 (84%)	22 (81%)	29 (91%)
Good	4 (9%)	4 (15%)	2 (6%)
Poor	3 (7%)	1 (4%)	1 (3%)

CRT/CH – conventional radiotherapy and chemotherapy; CRT – conventional radiotherapy; SCHRT – split course hypofractionated radiotherapy.

Supportive treatment

Systemic anticonvulsants (phenytoine or phenobarbital) were administered to all patients during irradiation. Steroids were given only as symptomatic medication required to control cerebral oedema.

Statistical methods

At the time of this analysis, 90 of 101 patients were known to have died. Estimates of survival were obtained by the product-limit method of Kaplan-Meier and comparisons were made by the log-rank test [5,6]. Both univariate and multivariate analyses were performed in order to detect prognostic factors, using the Cox proportional hazards model. The results are expressed as a hazard ratio with a 95% confidence interval [7]. The following prognostic variables were studied: age, gender, tumour location, extent of surgery, Karnofsky status (KS) and treatment schedule.

Results

Tolerance of irradiation

The tolerance was assessed according to the following criteria: very good – treatment without complications; good – periodic symptoms of increased intracranial pressure controlled pharmacologically with no breaks in irradiation; poor – the above symptoms which caused breaks in irradiation or its discontinuation. Radiotherapy was generally well tolerated; skin reactions in the SCHRT group were reported to be no more severe than those of the CRT regimen. Table 2 presents tolerance of irradiation according to treatment option.

Survival

Survival by treatment option is given in Figure 1.

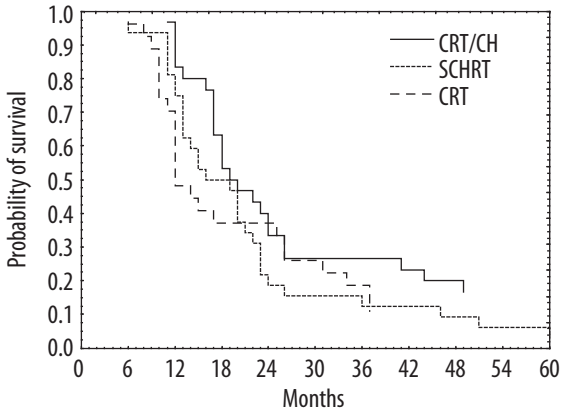

Figure 1. Survival by treatment option.

Table 3. Univariate analysis of prognostic factors.

Factors	MST	p
Age (years)		
45 or less	51	
More than 45	16	0.0016
Gender		
Male	25	
Female	23	NS
Tumour location		
Frontal	24	
Elsewhere	18	NS
Surgery		
Total resection	30	
Partial resection	20	NS
Karnofsky's status		
More than 60%	30	
60%	25	NS
Treatment option		
CRT/CH	35	
CRT	25	
SCHRT	30	NS

MST – median survival time in months; NS – statistically non-significant; CRT/CH – conventional radiotherapy and chemotherapy; CRT – conventional radiotherapy; SCHRT – split course hypofractionated radiotherapy.

The overall actuarial survival rates at 5 years in CRT/CH, CRT and SCHRT treatment groups were 10%, 11% and 6% respectively. The differences between survivals were not statistically significant.

Table 4. The definitive Cox model.

Factors	HR	CR 95%	p
Age (years)			
45 or less	1		
More than 45	3.06	1.89–4.30	0.0000
Surgery			
Total resection	1		
Partial resection	1.9	1.15–1.23	0.0624 (NS)

HR – hazard ratio; CR – confidence interval; NS – non-significant.

In Tables 3 and 4, univariate analysis of prognostic factors and the definitive Cox model are presented.

Discussion

Our observations of clinical population features of patients with AO are similar to those reported by other authors. The majority of patients were in the fifth and sixth decades of age and the most common site of tumour was the frontal lobe [8–10].

Our results are comparable to those described in the literature (Tables 5 and 6).

Numerous prognostic factors have been reported for AO, such as age, gender, performance status, neurological function, tumour location, extent of primary surgery, postoperative radiotherapy and/or chemotherapy, and molecular alterations, but no consensus has been obtained.

In our group of 101 patients with AO, only age was found to be an independent prognostic factor in determining overall survival. A better outcome in younger patients was reported in other series [8,11,12,13]. It is known that brain tumours in elderly patients seem to have an intrinsic resistance to cancer treatment; however, there is no clear explanation for this fact. The brain may have a unique role in the process of ageing; differentiated post-mitotic neurons are not replaced by cell division, and little turnover of DNA occurs in glial cells. Moreover, cell aging in the brain may be associated with a decrease in oxygen uptake. This may be related to the lower number of cytotoxic free radicals during irradiation, or to the difference existing in scavenging enzymes that neutralise or inactivate nucleophilic

Table 5. Results of postoperative irradiation and chemotherapy of anaplastic oligodendrogliomas.

Author	N	MST
Kryitsis et al. 1993 [11]	20	51
Kros 1994 et al. 1994 [12]	62	17
Kim et al. 1996 [13]	32	40
Deghani et al. 1998 [14]	24	12
Jeremic et al. 1999 [15]	18	36
Vanden Bent et al. 2006 [10]	185	40
Present series	42	35

MST – median survival time in months.

Table 6. Results of postoperative conventional irradiation of anaplastic oligodendrogliomas.

Author	N	MST
Smith et al. 1983 [16]	23	17
Mork et al. 1985 [17]	26	17
Shaw et al. 1992 [18]	55	38
Donahue et al. 1997 [19]	91	41
Paleoglos et al. 1999 [9]	36	27
Present series	27	25

MST – median survival time in months.

molecules [14]. Rosenblum et al. have shown that patient's age was inversely correlated with *in vitro* cell kill from a biopsy, and patients with sensitive cells were significantly younger than those with resistant cells [15]. Older people may have accumulated genetic damage throughout their lives, which is linked to exposure to exogenous mutagens and a possible decrease in various host functions, such as DNA repair and other defence mechanisms in normal tissues [16]. An attempt has been made to explain favourable diagnosis in younger patients by better tolerance of treatment, surgery as well as radiotherapy [17].

The extent of surgical resection has been reported to correlate with survival in patients with malignant gliomas. In our population composed of AO only patients, there was a trend toward longer survival with greater extent of resection, although the benefits of surgery did not reach statistical significance. The role of surgical resection in the management of patients with malignant gliomas remains controversial, despite the prospective randomized studies of BTSG demonstrating a significant impact of extent of surgery on median survival, even when adjusted for age, histology and performance status [18]. Based on our own experience we think that the impact of extent of surgery is difficult to ascertain due to the inadequate terminology used in surgical reports, which very often does not correlate with postoperative CT scan.

Gender and tumour location did not significantly affect survival in the present series. The influence of these factors in patients with AO has not been clearly established [3,8,9,19].

The Karnofsky performance status and parameters of neurological function did not significantly affect survival in our material. Besides, comparison of our results with others is difficult due to differences in the criteria used for assessment of neurological status. The same problem applies to performance status. In many series, neurological functional grade and/or Karnofsky score are important variables which have an impact on the survival time of patients [3,8,20–22]. On the other hand, there are reports which did not find any significant impact of these factors [9,12,19].The neurological status appears to be a better predictor than performance status. Assessment of status in patients with brain tumours by the Karnofsky score or WHO scale seems to be insufficient compared with neurological function. The neurological status can probably be more precise than the performance status, which is assessed second to neurological function.

Standard treatment for AO consists of maximum surgical resection and radiotherapy [1,3,9,12,13]. In the early 1990s it was recognized that some patients with these tumours demonstrated good response to systemic chemotherapy, particularly to the PCV (procarbazine, lomustine and vincristine) regimen [10,19–21,23]. This observation prompted two phase III trials. In the first (RTOG 9402) patients with AO were randomly assigned to receive either radiation therapy or up to 4 cycles of the PCV regimen followed by irradiation. In the second (EORTC 26951) patients were randomized to radiation therapy only, or to the same radiotherapy followed by six cycles of PCV chemotherapy. Both studies showed nearly identical results. They demonstrated no overall survival benefit when chemotherapy was added [10,24]. The two studies described above have not defined the standard first line treatment for patients with AO. Both approaches – the early use

of chemotherapy along with radiation treatment or waiting for tumour recurrence to start chemotherapy, thereby delaying the toxicities associated with these treatment regimens – should be considered acceptable. Determination of the presence or absence of 1p and 19q LOH (allelic loss of heterozygosity) should be mandatory because this finding has now been proven to have important prognostic and predictive power [13].

In our group of patients with AO, addition of chemotherapy with lomustine to the postoperative irradiation did not influence survival, but no definite conclusions regarding treatment efficacy can be drawn from the presented data. This study was done over a period of three decades during which changes in diagnostic techniques and clinical management were inevitable. Bias could be introduced by such factors and by the heterogeneity of treatment used in the described period, making it difficult to determine the true efficacy of the three presented treatment regimens.

Conclusions

The three different regimens used in our institution in the postoperative management of patients with anaplastic oligodendrogliomas were well tolerated. Conventionally fractionated radiotherapy with adjuvant chemotherapy provided approximately the same survival rates as radiation therapy alone, with overall five year survival of 10% and 11% respectively.

We do not recommend split course hypofractionated radiotherapy for these patients.

Age is the most important prognostic factor which significantly influences overall survival. Patients aged 45 years and less carried the best prognosis.

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